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International Searching Authority
Mr. A. Veronese (Examiner)
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Duitsland

√ FAX 00 49 89 2399 4465 + confirmation

Winksele, June 24, 2005

Re: International patent application PCT/BE2004/000121
Filing date: 25 August 2004
Applicant: K.U.Leuven Research & Development
Title: "Particle size reduction of bioactive compounds"
Our ref: K2326-PCT/go/td/av

To the Written Opinion dated January 4, 2005

Dear Mr. Veronese,

Please find enclosed the Demand form PCT/IPEA/401.

Please find enclosed without prejudice amended claims 1-32 replacing the claims currently on file.

Claim 1 has been amended by incorporating thereto the limitations of claims 8 and 19 as originally filed, and by specifying only the at least 25 % size reduction proportion present in original claim 1. The preferred size reduction proportions present in original claim 1 have now been introduced in amended claims 8 and 19, respectively. Consequently, original claim 14 has been deleted and the remaining claims from claim 19 onwards have been re-numbered accordingly. In each of claims 9-13 and 15, the reference to a fluid has been replaced with a reference to a liquid. In doing so, no new subject matter has been introduced.

With respect to item V of the written opinion, we comment each prior art document as follows:

USSR Patent No. 627,334 (**D1**) is enclosed in full text together with an English language translation thereof. It describes a milling system wherein a material to be grinded, such as flour, cacao powder (example 1) or a powdery medicinal compound (example 3), optionally together with grinding balls, is brought into a chaotic movement (" vortex motion ") by submitting said material and said optional balls to a swirling movement and a variable magnetic field superimposed on a DC magnetic field. It is assumed that particle size reduction in this system results at least partially from collisions between the material particles (and, optionally, balls). **D1** provides an improvement to a ball mill system wherein the swirling motion is complemented with the effects of a varying magnetic field on the movement of the material/balls. In the method of amended claim 1, particle size reduction is obtained by submitting particles suspended in a liquid to a linear movement through a magnetic field with a linear flow rate within a selected range. Thus particle size reduction resulting from collisions between the material particles cannot occur in the claimed invention like in **D1**, but particle size reduction is obtained by the effect of a linear movement through a magnetic field at a certain linear flow rate. **D1** therefore does not suggest any of the features of amended claim 1.

U.S. Patent No. 4,676,439 (**D2**) describes a pulverising apparatus, e.g. for fine ceramic particles of several microns in particle size (col. 1 lines 14-17), having a ball mill comprising electromagnets in order to ensure an optimal movement of the milling balls in the mill casing (see column 4 lines 40 to 50). The coarse-grain material is transported by a gas (col. 2 lines 40-41). Thus material to be ground is submitted to a rotary motion within a varying magnetic field. **D2** does not teach obtaining particle size reduction by suspending particles in a liquid and by the effect of linear movement through a magnetic field at a certain linear flow rate. **D2** therefore does not suggest any of the features of amended claim 1.

D3 describes a system for the micronisation of emulsion droplets, comprising a liquid stirring device, thus ensuring a rotary movement, and a magnetic field. **D3** does not teach reducing the particle size of solid particles suspended in a liquid by the combined action of linear movement through a magnetic field at a certain linear flow rate. **D3** therefore does not suggest any of the features of amended claim 1.

D4 describes a milling system wherein a powder to be milled is fed into a working chamber comprising 70 to 80% electromagnetic grinding objects which are brought into motion by a varying magnetic field. Therefore, the powder to be milled in the system of **D4** is submitted to a random movement resulting from collisions between the powder and the grinding objects. Particle size reduction resulting from collisions between the material particles probably does not occur in the claimed invention like in **D4**, but particle size reduction is obtained by the effect of a linear movement through a magnetic field at a certain linear flow rate. **D4** therefore does not suggest any of the features of amended claim 1.

D5 describes a ball mill system wherein the non-linear movement and impact efficiency of grinding balls are improved by using a variable electromagnetic field. **D5** does not mention the presence of a suspending liquid. Thus the system disclosed by **D5** appears to be comparable in its principle to the systems of **D1**, **D2** and **D4**. **D5** therefore does not suggest any of the features of amended claim 1.

Not a single prior art document suggests flowing the solid particles a linear movement through a magnetic field at a selected linear flow rate. Thus, even a combination of **D3** on the one hand (liquid system), and any of **D1**, **D2**, **D4** and **D5** on the other hand (suspension in a gas) would not provide the skilled person with a hint towards the invention defined in amended claim 1.

Very truly yours,

Ariane Bird

encl.: - claims 1-32 (4 pages), in triplicate
- form PCT/IPEA/401

CLAIMS

1. A method for reducing the average size of biologically active compound particles or agglomerates suspended in a liquid by flowing one or more times said liquid having biologically active compound particles or agglomerates suspended therein through one or more magnetic fields to reduce the average size of a substantial portion of the biologically active compound particles or agglomerates by at least 25%, wherein the linear flow rate of said liquid through each said magnetic field is between 0.25 and 25 m/s.

2. A method according to claim 1, wherein the strength of each said magnetic field is at least about 2,000 gauss.

3. A method according to claim 1 or claim 2, wherein the average size of said biologically active compound agglomerates before performing said method is in a range from about 10 µm to about 100 µm.

4. A method according to any of claims 1 to 3, wherein the average size of a substantial portion of said biologically active compound agglomerates after performing said method is reduced to a range from about 0.45 µm to 5 µm.

5. A method according to any of claims 1 to 4, wherein said substantial portion is at least 50% by weight of the suspended agglomerates.

6. A method according to any of claims 1 to 5, wherein the average particle size of said biologically active compound particles before performing said method is in a range from about 0.5 µm to about 10 µm.

7. A method according to any of claims 1 to 6, wherein the average particle size of said biologically active compound particles after performing is reduced to a range from about 0.5 nm to about 500 nm.

8. A method according to any of claims 1 to 7, wherein the average size of a substantial portion of the biologically active compound particles or agglomerates is reduced by at least 50%.

9. A method according to any of claims 1 to 8, wherein said liquid is water.

10. A method according to any of claims 1 to 8, wherein said liquid is an organic solvent or a combination thereof with water.

11. A method according to any of claims 1 to 10, wherein said biologically active compound particles or agglomerates are suspended in said liquid in the form of a slurry and the concentration of said biologically active compound particles or agglomerates in said liquid is at least two times the solubility limit of said biologically active compound in said liquid under the physical (temperature, pressure) and chemical (pH) conditions prevailing while flowing said slurry through said magnetic field.

12. A method according to any of claims 1 to 11, wherein flowing said liquid through said magnetic field is effected at a temperature between the freezing temperature and the boiling temperature of said fluid under the pressure prevailing while flowing said fluid through said magnetic field.

13. A method according to any of claims 1 to 12, wherein flowing said liquid through said one or more magnetic fields is effected at a temperature between about 2°C and 95°C under atmospheric pressure.

14. A method according to any of claims 1 to 7, wherein the average size of a substantial portion of the biologically active compound particles or agglomerates is reduced by at least 80%.

15. A method according to any of claims 1 to 14, wherein said liquid includes one or more stabilizing agents.

16. A method according to claim 15 wherein the stabilizing agent is a surfactant, a polymer, a silicate, a hydrophilic agent or a combination thereof.

17. A method according to claims 15 or 16, wherein said stabilizing agent comprises a surfactant in an amount such as to produce surfactant-capped nanoparticles.

18. A method according to any of claims 1 to 17, wherein said fluid is re-circulated two or more times through said one or more magnetic fields.

19. A method according to any of claims 1 to 18, wherein the residence time of said liquid through each said magnetic field is between 60 microseconds and 10 seconds.

20. A method according to any of claims 1 to 19, wherein the biologically active compound is in a crystalline form.

21. A method according to any of claims 1 to 19, wherein the biologically active compound is in an amorphous form.

22. A method according to any of claims 1 to 21, wherein the biologically active compound is a drug classifiable as Class II or Class IV of the Biopharmaceutical Classification System.

23. A method according to any of claims 1 to 22, wherein the biologically active compound is a drug having a water-solubility below about 2 mg/ml.

24. A method according to any of claims 1 to 23, wherein the biologically active compound is a drug having a water-solubility below about 5 µg/ml.

25. A method according to any of claims 1 to 24, wherein the biologically active compound is a cosmetic agent, a diagnostic agent, a herbicide, an insecticide, a biocide or a fungicide.

26. A process for manufacturing a biologically active compound formulation, the said process involving the use of biologically active

compound particles or agglomerates, comprising a step of reducing by at least 25% the average size of a substantial portion of said biologically active compound particles or agglomerates, wherein said step includes a method according to any of claims 1 to 25.

27. A process according to claim 26, wherein said process further comprises one or more post-processing steps performed following the size reducing step.

28. A process according to claim 26 or claim 27, wherein said post-processing step is a drying step for substantially removing the liquid in which the biologically active compound particles or agglomerates are suspended during the size reducing step.

29. A process according to claim 28, wherein said drying step comprises freeze drying.

30. A process according to claim 28, wherein said drying step comprises spray drying.

31. A process according to any of the claims 26 to 30, wherein said post-processing step is a step of mixing an adjuvant together with the optionally dried particles or agglomerates with reduced size.

32. A population of biologically active compound particles obtained by a method according to any of claims 1 to 25 or a process according to any of claims 26 to 31.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: K2365-PCT

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/BE2004/000121	25 August 2004 (25.08.2004)	26 August 2003 (26.08.2003)

Title of invention: Particle size reduction of bioactive compounds

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

K.U.LEUVEN RESEARCH & DEVELOPMENT
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Facsimile No.: +32-16-32 65 15
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
BE	BE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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State *(that is, country)* of nationality:	State *(that is, country)* of residence:
BE	BE

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/BE2004/000121

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NUYENS, Jan
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Belgium

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
BE	BE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/BE2004/000121

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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Agent's registration No. with the Office

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[ ] the international application as originally filed

the description
- [X] as originally filed
- [ ] as amended under Article 34

the claims
- [ ] as originally filed
- [ ] as amended under Article 19 (together with any accompanying statement)
- [X] as amended under Article 34

the drawings
- [X] as originally filed
- [ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

- [X] which is the language in which the international application was filed.
- [ ] which is the language of a translation furnished for the purposes of international search.
- [ ] which is the language of publication of the international application.
- [ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects **all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

Sheet No. .4.

International application No.
PCT/BE2004/000121

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

				For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:		sheets	☐	☐
2. amendments under Article 34	:	4	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:		sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:		sheets	☐	☐
5. letter	:	3	sheets	☐	☐
6. other *(specify)*	:		sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listings in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

ARIANE BIRD

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

CONFIRMATION OF THE PAYMENT
24 JUN 2005

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/BE2004/000121	For International Preliminary Examining Authority use only
Applicant's or agent's file reference K2326-PCT	Date stamp of the IPEA

Applicant
K.U.LEUVEN RESEARCH & DEVELOPMENT

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	EUR 1530,- P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EUR 129,- H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1.659,- TOTAL	

MODE OF PAYMENT

- [X] authorization to charge deposit account with the IPEA (see below)
- [ ] cheque
- [ ] postal money order
- [ ] bank draft
- [ ] cash
- [ ] revenue stamps
- [ ] coupons
- [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EPO

- [X] Authorization to charge the total fees indicated above.
- [ ] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 28020053

Date: 24 June 2005

Name: Ariane Bird

Signature: A. Bird